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Pharmacotherapy

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THEORY/CONCEPTUAL FRAMEWORK

Posttraumatic stress disorder (PTSD) appears to be a very complex disorder that is associated with stable and profound alterations in many psychobiological systems that have evolved for coping, adaptation, and survival of the human species (Friedman, 1999; Friedman, Charney, & Deutch, 1995; Rasmusson & Charney, 1997; Yehuda & McFarlane, 1997). Given the number of fundamental psychobiological systems that appear to be altered, it may be that PTSD is not a unitary psychobiological abnormality but that (as with fever and edema) there are a number of possible mechanisms through which this disorder might evolve. Another possibility is that there are different psychobiological subtypes of a common PTSD disorder. Indeed, some investigators have concluded that because of this complexity, there is no single animal model that is applicable to PTSD (Rasmusson & Charney, 1997).

Table 5.1 summarizes psychobiological abnormalities in PTSD that involve specific neurotransmitter, neurohormonal, or neuroendocrine systems. Such information is relevant to understanding why certain drugs might be effective therapeutic agents. It might also guide the development of future drugs designed specifically for use in PTSD. Ideally, such an approach would lead to rational pharmacotherapy in which specific classes of drugs are selected because of their actions on specific psychobiological systems. As we consider PTSD from this conceptual perspective, it should be kept in mind

TABLE 5.1. Psychobiological Abnormalities Possibly Associated with PTSD

Proposed psychobiological abnormality	Possible clinical effect
Adrenergic hyperreactivity	Hyperarousal, reexperiencing, dissociation, rage/aggression abnormal information/memory processes, panic/anxiety
Hypothalamic–pituitary–adrenocortical enhanced negative feedback	Stress intolerance
Opioid dysregulation	Numbing
Elevated corticotropin-releasing factor levels	Hyperarousal, reexperiencing, panic/anxiety
Sensitization/kindling	Hyperarousal, reexperiencing
Glutamatergic dysregulation	Dissociation, impaired information and memory processing
Serotonergic dysregulation	Numbing, reexperiencing, hyperarousal, poorly modulated stress responses, associated symptoms[a]
Increased thyroid activity	Hyperarousal

[a]Associated symptoms: Rage, aggression, impulsivity, depression, panic/anxiety, obsessional thoughts, chemical abuse/dependency.

that most of our current information about pharmacotherapy for PTSD is based on empirical trials with established antidepressant and anxiolytic drugs rather than agents specifically targeting putative neurobiological mechanisms underlying the pathophysiology of PTSD.

Some proposed psychobiological abnormalities listed in Table 5.1 are well established (e.g., adrenergic hyperreactivity and hypothalamic–pituitary–adrenocortical [HPA] enhanced negative feedback). Other proposed mechanisms have little empirical support or are primarily theoretical and can only be considered speculative at this time. This is a large and rapidly expanding area of research. More details can be found elsewhere (Friedman, 1999; Friedman, Charney & Deutch, 1995; Yehuda & McFarlane, 1997). We present the following very brief summary of current research findings that may be relevant to pharmacotherapy for PTSD:

1. Adrenergic hyperreactivity appears to be associated with hyperarousal, reexperiencing, panic/anxiety symptoms, and probably associated with dissociation and rage/aggression. Adrenergic mechanisms also play a key role in processing traumatic memories. An alpha-2 adrenergic agonist such as clonidine or a beta-adrenergic antagonist such as propranolol might be expected to attenuate this abnormality. Tricyclic antidepressants (TCAs)

and monoamine oxidase inhibitors (MAOIs) also reduce adrenergic activity through more indirect mechanisms. As shown in studies on treatment of panic disorder, the antiadrenergic effects of both TCAs and MAOIs can be clinically significant.

2. HPA-enhanced negative feedback is a well-established alteration that has not been linked to a specific clinical abnormality. One speculation is that this may be associated with the low tolerance for stress seen in PTSD patients but no data support this hypothesis. Drugs that act on either the adrenergic or serotonergic systems might normalize HPA function.

3. It has been hypothesized that opioid dysregulation might be associated with psychic numbing. In one study, narcotic antagonists appeared to reduce numbing in some patients but produced increased reexperiencing and hyperarousal symptoms for others (Glover, 1993).

4. Elevated corticotropin-releasing factor (CRF) may, etiologically, be the most important abnormality in PTSD because of its central role in the human stress response. Since CRF is uniquely positioned to simultaneously ignite a cascade of adrenergic, HPA, immunological, and other biological responses to stress, appropriate treatment, theoretically, might be to blockade CRF's actions with CRF antagonists or other drugs that inhibit these actions. This is an important area for further research.

5. Sensitization and kindling result when repeated exposure to the same stimulus produces a progressive intensification of neurophysiological, behavioral, or psychobiological response. Sensitization/kindling has been proposed (Post, Weiss, & Smith, 1995) as an animal model for PTSD. Anticonvulsant agents such as carbamazepine and valproate have been suggested as PTSD treatments specifically because of their antikindling properties. There is also interest in the possibility that the new anticonvulsant, lamotrigene, will also have a clinically significant antikindling effect.

6. Glutamatergic dysregulation has been postulated as etiologically responsible for dissociation and for the information- and memory-processing abnormalities associated with PTSD. Normalization could theoretically be achieved with newer anticonvulsants (such as lamotrigene) that modulate glutamatergic transmission (Krystal, Bennett, Bremner, Southwick, & Charney, 1995).

7. As noted in Table 5.1, serotonin (5-HT) appears to have a direct or indirect role in mediating a number of core (DSM-IV B, C, and D) PTSD as well as associated, clinically relevant symptoms. This may be why selective serotonin reuptake inhibitors (SSRIs) have shown such early promise as effective drugs for PTSD. SSRIs might also normalize the poor modulation of the stress response that is associated with a serotonin deficiency (Weissman & Harbert, 1972).

8. Although elevated in PTSD, increased thyroid activity is usually in the high normal rather than thyrotoxic range. Therefore, it would probably be inadvisable to consider an antithyroid agent but, rather, to consider using

a beta-adrenergic antagonist such as propranolol to reverse hyperarousal symptoms due possibly to this abnormality.

THE TECHNIQUE OF PHARMACOTHERAPY

The major techniques in pharmacotherapy involve (1) selecting a drug whose pharmacological actions might be expected to normalize the psychobiological abnormalities associated with a specific disorder; (2) choosing the most appropriate therapeutic agent based on proven efficacy against a specific symptom, cluster of symptoms, and/or comorbid disorder; (3) monitoring and readjusting the dosage in order to optimize therapeutic efficacy and onset of action while minimizing the likelihood of side effects; and (4) knowing when there has been an adequate therapeutic trial of a given drug in order to supplement treatment with an additional drug or to switch to a different pharmacological agent.

There is a strong rationale for pharmacotherapy as an important treatment in PTSD. As noted previously, a number of animal models and neurobiological mechanisms seem pertinent to this disorder. In addition, PTSD patients exhibit abnormalities in several key neurobiological systems (see Table 5.1). Furthermore, there is considerable overlap of symptoms between PTSD, depression, and other anxiety disorders. Finally, PTSD is frequently comorbid with psychiatric disorders that are responsive to drug treatment (e.g., major depression and panic disorder). Drug treatment is one of the most feasible treatments for PTSD. It is generally accepted by most patients although the occurrence of side effects, lack of patient compliance with prescribed drug regimens, and the high commercial cost of new therapeutic agents (e.g., SSRIs, nefazodone, valproate, etc.) may diminish feasibility.

The cost of drug treatment is difficult to compare with the cost of psychotherapy, since it depends on the duration of treatment, the cost of the drug itself, and many other factors. Compliance is generally good during the initial weeks of treatment; it may remain high if there is clinical improvement, but it also may not, even if there is a favorable response to medication. Finally, although it is very easy to disseminate the necessary information about drug treatment to prescribing physicians, it is quite difficult to detect and correct improper prescribing practices.

PTSD is often associated with at least one comorbid psychiatric disorder (e.g., depression, other anxiety disorders and/or chemical abuse/dependency). It is often also associated with clinically significant disruptive symptoms (e.g., impulsivity, mood lability, irritability, aggressiveness and/or suicidal behavior). Some of the drugs to be reviewed in this practice guideline have proven or probable efficacy in ameliorating some of these comorbid disorders or associated symptoms when they, not PTSD, have been the primary targets for treatment. (It should be emphasized, however, that there are scarcely any published

findings regarding PTSD drug trials in which comorbid disorders or associated symptoms were systematically controlled and evaluated). Ideally, a practicing pharmacotherapist would select a drug that might be expected to ameliorate such comorbid disorders and associated symptoms at the same time that it reduces PTSD symptom severity. This is pharmacotherapeutic technique at its best.

Because of the many biological abnormalities presumed to be associated with PTSD (Table 5.1), and because of the overlap between symptoms of PTSD and other comorbid disorders, almost every class of psychotropic agent has been administered to PTSD patients. Based on the published data, the following classes of drugs are reviewed in this chapter: SSRIs, other serotonergic agents, antiadrenergic agents, MAOIs, TCAs, benzodiazepines, anticonvulsants, and antipsychotics. Their clinical and pharmacological actions are discussed in a later section.

METHODS OF COLLECTING DATA

These practice guidelines were developed after a comprehensive literature review of all randomized clinical trials (RCTs), open trials, and case reports on pharmacotherapy for PTSD included in PILOTS. The search was conducted using the following keywords: PTSD, pharmacotherapy, antidepressants, anxiolytics, antiadrenergic agents, anticonvulsants, and antipsychotics, as well as the specific names of each drug mentioned in this report. Data from RCTs were given the greatest weight; such findings are summarized in Table 5.2 and include effect sizes for each RCT. Table 5.3 is much more inclusive and summarizes results from all drug trials because of the theoretical as well as clinical interest generated by such data. Table 5.4 presents our recommendations on drug treatment, the strength of the published evidence, indications, and contraindications.

SUMMARY OF THE LITERATURE

Evidence from Randomized Clinical Trials

A summary of randomized clinical drug trials is shown in Table 5.2. Results have clearly been mixed. Given the fact that study populations differed with respect to trauma type, severity, and chronicity, as well as gender, veteran status, outcome measures, and (probably) comorbidity, it is difficult to make any generalizations with confidence. Three studies with clinically meaningful effect sizes (e.g., approximately 1.0) involve an MAOI (phenelzine), and two trials with an SSRI (fluoxetine). Modest improvements were seen with a TCA

TABLE 5.2. Randomized Clinical Trials of PTSD: Drug versus Placebo Treatment

Drug[a]	Class	*n*	Duration (wk)	Subjects	Sex	Outcome	Drug–placebo response rates[b]	Drug–placebo differences[b]	PTSD-specific drug effects[c]	Effect size[c]
Amitriptyline[1]	TCA	46	8	Mil	M	IES total	47%/19%	28%	+	0.64
Desipramine[2]	TCA	18	4	Mil	M	IES avoidance	2%/0%	2%	–	0.16
Desipramine[2]	TCA	18	4	Mil	M	IES intrusion	4%/1%	3%	–	0.05
Imipramine[3]	TCA	60	8	Mil	M	IES total	65%/28%	37%	–	0.25
Phenelzine[3]	MAOI	60	8	Mil	M	IES total	68%/28%	40%	++	1.08
Phenelzine[4]	MAOI	13	4	Mil/civ	?	IES total	35%/36%	0%	–	0.10
Brofaromin[5d]	MAOI/SSRI	113	10	Mil/civ	M/F	CAPS total	60%/40%	18%	–	0.01
Brofaromine[6d]	MAOI/SSRI	45	14	Civ/mil	M/F	CAPS total	52%/29%	23%	+	0.52
Fluoxetine[7e]	SSRI	24	5	Mil	M	CAPS	15%/10%	5%	–	0.37
Fluoxetine[7e]	SSRI	23	5	Civ	F/M	CAPS	41%/21%	20%	++	1.12
Fluoxetine[8]	SSRI	53	12	Civ	F	CGI	85%/62%	23%	++	0.92
Sertraline[9]	SSRI	208	12	Civ	F/M	DTS	60%/39%	21%	++	0.40
Sertraline[10]	SSRI	187	12	Civ	F/M	CAPS	55%/35%	20%	++	0.30
Alprazolam[11]	BZD	10	5	Mil/civ	?	IES total	14%/4%	10%	–	0.28
Inositol[12]	2nd Mess	13	4	Mil/civ	M/F	IES total	11%/0%	11%	–	0.25

Note. TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; BZD, Benzodiazepine; 2nd Mess, second messenger; IES, Impact of Event Scale; CAPS, Clinician-Administered PTSD Scale; CGI, Clinical Global Improvement Scale; DTS, Davidson Trauma Scale.

[a]References to studies: 1. Davidson et al. (1990); 2. Reist et al. (1989); 3. Kosten et al. (1991); 4. Shestatzky, Greenberg, & Lerer (1988); 5. Baker et al. (1995); 6. Katz et al. (1994/1995); 7. van der Kolk et al. (1994); 8. Davidson et al. (1997); 9. Davidson, Malik, & Sutherland (1996); 10. Brady et al. (2000); 11. Braun et al. (1990); 12. Kaplan et al. (1995).

[b]From Davidson et al. (1997).

[c]From Friedman (1997).

[d]Not available commercially.

[e]Drug–placebo response rates approximated from a graph.

(amitriptyline; effect size = 0.64) and an MAOI/SSRI (brofaromine; effect size = 0.52).

The two largest studies are multisite RCTs with the SSRI sertraline, which tested approximately 200 subjects in each trial. Although effect sizes were modest, drug–placebo differences in both studies were highly significant ($p < .001$), showing that sertraline reduced PTSD DSM-IV B, C, and D symptoms (Brady et al., 2000; Davidson et al., 1997). The positive findings from these large studies impressed the United States Food and Drug Administration (FDA) sufficiently so that sertraline was approved in December 1999 as an indicated treatment for PTSD. It is the first and only medication to receive such FDA approval. Therefore, the strength of evidence favoring the efficacy for sertraline is given a full Agency for Health Care Policy and Research (AHCPR) Level A rating at this time (see Table 5.4). On the other hand, the mixed results from the small, randomized clinical trials with fluoxetine (van der Kolk et al., 1994) indicate an AHCPR Level A/B rating is appropriate for that drug at this time.

In summary, dramatic responses to medication have been the exception rather than the rule. MAOIs and SSRIs have been more successful than other drugs. It is important to recognize that there have been negative as well as positive clinical trials with SSRIs, MAOIs, and TCAs. Most notably, there have been negative RCTs with phenelzine, desipramine, fluoxetine, and alprazolam, as shown in Table 5.2. Many of the marginal or negative results may have been due to methodological factors (e.g., research design, subjects tested, treatment duration, outcome instruments, etc.) rather than because the drugs, themselves, are ineffective. We have many more questions than answers at this time. Much more research is definitely needed to clarify these questions.

Other Evidence: Open Trials and Case Reports

A fair number of open trials and case reports have been published in addition to randomized clinical trials. As shown in Table 5.3, evidence for the efficacy of many drugs can only be found in these open trials and case reports.

Selective Serotonin Reuptake Inhibitors

In addition to RCTs with sertraline and fluoxetine, which effectively reduce all clusters (DSM-IV B, C, and D) of PTSD symptoms and produce clinical global improvement (Davidson, Malik, & Sutherland, 1997) a number of successful open trials and case reports have been published concerning SSRIs such as fluoxetine, sertraline, paroxetine, and fluvoxamine (see Friedman, 1996, for references). In general, investigators have been impressed by the capacity of SSRIs to reduce the numbing symptoms of PTSD, since other drugs tested thus far do not seem to have this property. In recent, open-label studies with sertraline in rape trauma survivors (Rothbaum, Ninan, &

TABLE 5.3. Summary of Published Results on Pharmacotherapy for PTSD

Drug class	Specific drugs	Daily dose	Probable mechanism of action	No. of RCT	Remarks
SSRIs	Sertraline	50–200 mg	SSRI	2	Whereas earlier studies suggested that SSRIs were primarily effective on DSM-IV PTSD numbing (C) symptoms, more recent RCT and open trials suggest that they produce global improvement and reduce all PTSD (B, C, D) symptom clusters. They are also effective in comorbid disorders such as depression, panic disorder, obsessive–compulsive disorder and chemical dependency/abuse. Finally SSRIs may reduce symptoms associated with PTSD such as rage, impulsivity, suicidal thoughts, depressed mood, obsessional thinking, and alcohol/drug behavior.
	Fluoxetine	20–80 mg	SSRI	3	
	Fluvoxamine	250–300 mg	SSRI	0	
	Paroxetine	10–40 mg	SSRI	0	
Other	Trazodone	25–500 mg	SSRI/5-HT_2 blockade	0	Often combined with SSRIs to reverse SSRI-induced insomnia. In one small, open trial, trazodone reduced B, C, and D symptoms. A large multisite randomized clinical trial is underway.
	Nefazodone	100–600 mg		0	Results from two published open-label studies suggest that nefazodone produces global improvement, better sleep, and anxiety reduction in PTSD patients.
Serotonergic	Cyproheptadine	4–28 mg	5-HT antagonist	0	Anecdotal reports indicate that it suppresses nightmares and flashbacks.
	Buspirone	30–60 mg	5-HT_1A partial agonist	0	A few case reports suggest reduced B and D symptoms.
Antiadrenergic	Clonidine	0.2–0.6 mg	Alpha-2 agonist	0	Reduces B and D symptoms. Patients may become tolerant.
	Guanfacine	1–3 mg	Alpha-2 agonist	0	Promising case reports in patients who had become tolerant to clonidine.
	Propranolol	40–160 mg	Beta blocker	A-B-A	Successful A-B-A study in which B and D symptoms were reduced in children with sexual-/physical-abuse-related PTSD. Two other studies with mixed results.

(*continued*)

TABLE 5.3. *(continued)*

Drug class	Specific drugs	Daily dose	Probable mechanism of action	No. of RCT	Remarks
MAOIs	Phenelzine	45–75 mg	Irreversible	2	Good global improvement and reduction of intrusive recollection (B) symptoms and some efficacy against C symptoms. Patients must adhere to MAOI dietary restrictions.
	Tranylcypromine	20–40 mg	MAOI	0	Positive case report—little data.
	Isocarboxazide[a]	10–30 mg	MAOI	0	Positive case report—little data.
	Moclobemide	300–600 mg	Reversible MAO-A inhibitor	0	One open trial—reduced B and C symptoms.
TCAs	Imipramine	150–300 mg	NE/5-HT	1	Not as potent as MAOIs but similar action profile.
	Amitriptyline		reuptake	1	Good global improvement and reduction of B symptoms.
	Desipramine		inhibitors	1	Amitriptyline most effective against C symptoms. Desipramine was ineffective in a randomized clinical trial.
Benzodiazepines (BZD)	Alprazolam	0.5–6 mg	BZD agonist	1	Few studies. No effect on B or C symptoms. Reduce insomnia, anxiety, and irritability. Clinically significant withdrawal syndrome.
	Clonazepam	1–6 mg	BZD agonist	0	
Anticonvulsants	Carbamazepine	600–1,000 mg	Antikindling	0	Carbamazepine effective on B and D symptoms. Valproate effective on C and D symptoms.
	Valproate	750–1,750 mg	action	0	
Antipsychotics	Thioridazine	200–800 mg	D_2 antagonist	0	Case reports—effective on B and D symptoms.
	Clozapine		5HT2/D2	0	
	Risperidone		antagonist		

[a]No longer commercially available.

Thomas, 1996), fluvoxamine in Vietnam combat veterans (Marmar et al., 1996), and paroxetine in nonveterans with a mixture of traumatic experiences (e.g., rape, criminal assault, and accidents; Marshall et al., 1998), all three clusters (reexperiencing, avoidant/numbing and hyperarousal) of PTSD symptoms were dramatically reduced by SSRI treatment. The paroxetine and fluvoxamine studies are particularly noteworthy because the veterans complained very little about insomnia or arousal side effects, as has been the case with other SSRIs tested. Although SSRIs are generally regarded as having fewer side effects than other drugs, some patients cannot tolerate them because of gastrointestinal symptoms and sexual dysfunction in addition to insomnia and agitation.

SSRIs are also an attractive choice because they may improve comorbid disorders such as depression, panic, and obsessive–compulsive disorder, and reduce alcohol consumption (Brady, Sonne, & Roberts, 1995).

SSRIs may also be clinically useful because a number of symptoms associated with PTSD may be mediated by serotonergic mechanisms such as rage, impulsivity, suicidal intent, depressed mood, panic symptoms, obsessional thinking, and behaviors associated with alcohol or drug abuse/dependency (Fava et al., 1996; Friedman, 1990).

Other Serotonergic Agents

As shown in Table 5.3, there have been two open-label trials with nefazodone but very few data on trazodone, cyproheptadine, and buspirone. Nefazodone, an SSRI plus 5-HT_2 antagonist, has shown promise in open-label trials of combat veterans and may be of particular help in improving sleep and decreasing anger (Davidson, Weisler, Malik, & Conner, 1998; Hertzberg, Feldman, Beckham, Moore, & Davidson, 1998). Trazodone (which is also an SSRI plus 5-HT_2 antagonist) has shown only modest effectiveness against PTSD symptoms in a small open trial (Hertzberg, Feldman, Beckham, & Davidson, 1996) but has been prescribed mostly because of its capacity to reverse the insomnia caused by SSRI agents such as fluoxetine and sertraline. As a result, many PTSD patients receiving SSRI treatment also receive trazodone (25–500 mg) at bedtime. Trazodone's advantage over conventional hypnotics is that its major serotonergic mode of action is synergistic with overall SSRI treatment and its sedative properties promote sleep (Cook & Conner, 1995).

Antiadrenergic Agents: Propranolol, Clonidine, and Guanfacine

Although it is well established that adrenergic dysregulation is associated with chronic PTSD (for details and references, see Friedman, Charney, & Deutch, 1995; Yehuda & McFarlane, 1997), there has been little research with the alpha-2 agonist, clonidine, or with the beta adrenergic antagonist, propra-

nolol, despite the fact that positive findings with both drugs were reported as early as 1984 (Kolb, Burris, & Griffiths, 1984). Indeed, there are no randomized clinical trials with either drug.

In four open trials with clonidine (see Friedman & Southwick, 1995, for references), successful reduction of many PTSD and associated symptoms was observed, including traumatic nightmares, intrusive recollections, hypervigilance, insomnia, startle reactions, and angry outbursts; in addition, patients in these trials reported improved mood and concentration.

Sometimes, patients who have a favorable initial response to clonidine appear to develop tolerance to this drug, resulting in a return of PTSD symptoms. There are two recent case reports in which clonidine was replaced by the adrenergic alpha-2 agonist, guanfacine (which has a longer half-life, 18–22 hours), after tolerance had developed. In both cases, complete suppression of PTSD symptoms was again achieved and maintained over the subsequent course of treatment (Harmon & Riggs, 1996; Horrigan, 1996).

In an A-B-A design (6 weeks off–6 weeks on–6 weeks off medication), propranolol was administered to eleven physically and/or sexually abused children with PTSD. Significant reductions in reexperiencing and arousal symptoms were observed during drug treatment but symptoms relapsed to pretreatment severity following discontinuation of medication (Famularo, Kinscherff, & Fenton, 1988). Results were mixed in two other trials with propranolol.

Monoamine Oxidase Inhibitors

In addition to two randomized clinical trials with phenelzine (one of which had serious methodological flaws) reported previously, there have been two successful open trials of phenelzine, a number of positive case reports (see De Martino, Mollica, & Wilk, 1995, for references), and one negative open trial with phenelzine (Weizman et al., 1996).

A comprehensive review of all published findings on MAOI treatment (Southwick, Yehuda, Giller, & Charney, 1994) found that MAOIs produced moderate to good global improvement in 82% of all patients, primarily due to reduction in reexperiencing symptoms such as intrusive recollections, traumatic nightmares, and PTSD flashbacks. Insomnia also improved. No improvement was found, however, in PTSD avoidant/numbing, PTSD hyperarousal, and depressive or anxiety/panic symptoms.

The use of MAOIs has traditionally been limited when there are legitimate concerns that patients may ingest alcohol or pharmacologically contraindicated illicit drugs, or that they may not adhere to necessary dietary restrictions. The most serious consequence of lack of compliance is a hypertensive crisis, which is a medical emergency. Such concerns do not apply to reversible MAO-A inhibitors such as moclobemide (which are not currently available in the United States). Indeed, moclobemide produced significant

reductions in PTSD reexperiencing and avoidant symptoms in a recent open trial with 20 patients (Neal, Shapland, & Fox, 1997).

Tricyclic Antidepressants

In addition to the randomized clinical trials (showing positive results with imipramine and amitriptyline, and negative results with desipramine) reported previously, there are numerous case reports and open trials with TCAs (see Ver Ellen & van Kammen, 1990, for references). Results have been mixed and generally modest in magnitude. In their analysis of 15 randomized trials, open trials, and case reports involving TCA treatment for PTSD, Southwick and associates (1994) found that 45% of patients showed moderate to good global improvement following treatment, whereas MAOIs produced global improvement in 82% of patients who received them. As with MAOIs, most improvement was due to reductions in reexperiencing rather than avoidant/numbing or arousal symptoms.

To summarize, TCAs appear to reduce PTSD reexperiencing and/or avoidant symptoms but have not demonstrated the same degree of efficacy as SSRIs or MAOIs. Furthermore, their side effects are not tolerated well by many PTSD patients. It is because of their relative lack of potency, their side effects, and their failure to reduce avoidant/numbing symptoms that TCAs have been replaced by SSRIs as first-line drugs in PTSD treatment. This may be a rush to judgment, however, since TCAs have been tested primarily on veterans with severe and chronic PTSD, while SSRIs have been tested mostly on nonveteran cohorts. Indeed, TCAs have actually outperformed SSRIs in reducing PTSD severity among combat veterans (Davidson et al., 1997).

Benzodiazepines

There are only three publications on benzodiazepine treatment for PTSD in addition to the randomized clinical trial with alprazolam reported previously (Braun et al., 1990). These include open trials with alprazolam and clonazepam, respectively. In each study, however, patients reported reduced insomnia, anxiety, and irritability but no improvement in PTSD reexperiencing, avoidant, or numbing symptoms. In addition, there is a risk of prescribing these agents for many patients with comorbid alcohol or drug abuse/dependence, and a serious withdrawal syndrome has been reported following abrupt discontinuation of alprazolam among PTSD patients (see Friedman & Southwick, 1995).

In summary, the evidence does not support benzodiazepines as first-line treatment for PTSD. A preliminary open-label report in which the benzodiazepine hypnotic, temazepam, was administered at bedtime to trauma survivors with acute stress disorder (e.g., 1 to 3 months after the traumatic event)

found that pharmacotherapy specifically targeting disrupted sleep was associated with marked reduction in PTSD symptoms (Mellman, Byers, & Angenstein, 1998). On the other hand, a prospective study with alprazolam and clonazepam in recently traumatized emergency room patients found that early treatment with benzodiazepines did not appear to prevent the later development of PTSD (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996).

Anticonvulsants

There have been a number of open trials of anticonvulsant drugs with PTSD patients initially tested because of their antikindling action. In five studies, carbamazepine produced reductions in reexperiencing and arousal symptoms, while in three studies, valproate produced reductions in avoidant/numbing and arousal (but not reexperiencing) symptoms (see Friedman & Southwick, 1995, for references).

Antipsychotics

The current thinking is that antipsychotic medications should only be prescribed for the rare PTSD patients who fail to respond to other drugs and who exhibit psychotic symptoms. Some preliminary anecdotal observations have shown that PTSD patients who exhibit extreme hypervigilance/paranoia, physical aggression, social isolation, and trauma-related hallucinations, and are refractory to SSRIs, antiadrenergics, and other drugs described previously (see Friedman & Southwick, 1995), may respond to antipsychotic agents such as thioridazine (Dillard, Bendfeldt, & Jernigan, 1993) and clozapine (Hamner, 1996). Further reports can be expected in the future, especially with atypical antipsychotic drugs such as olanzapine, risperidone, and quetiapine, because clinicians have begun to prescribe them for refractory PTSD patients.

AREAS REQUIRING FURTHER EXPLORATION

Although there are promising results with a number of drugs, much more research is needed. Among the important questions that demand additional attention are the following:

1. Has generalizing too much from results with the most chronic, severe, and treatment refractory patients led us to underestimate the potential usefulness of pharmacotherapy in PTSD?
2. Have we been utilizing the best outcome measures (e.g., should we pay more attention to clinical global improvement, functional improvement, and clinical utilization rather than PTSD symptom reduction)?

3. Should we consider new kinds of pharmacological agents rather than established antidepressant/anxiolytic agents that were not developed initially for the treatment of PTSD)? Consideration of the unique pathophysiology of PTSD would suggest that drugs acting on key mechanisms of the human stress response, itself, might have potential usefulness in PTSD treatment. This might include currently experimental drugs that reduce the actions of CRF, such as CRF antagonists, neuropeptide Y agonists, or drugs that enhance the actions of neuropeptide Y.

4. Are there different subtypes of PTSD that might require different drugs for treatment? Clinical evidence suggests that there may be depressive and anxious subtypes of PTSD. Laboratory findings suggest that there may be subtypes of PTSD that specifically involve adrenergic versus serotonergic mechanisms. Evidence from sensitization and kindling models of PTSD (Post, Weiss, & Smith, 1995) have demonstrated that the psychobiology of stress-induced abnormalities changes over time, suggesting that some drugs might be effective in early stages of the disorder while different drugs might be more effective in chronic PTSD. Finally, the clinical phenomenology of complex PTSD (Herman, 1992, with the prominence of impulsive, dissociative, and somatic symptomatology, suggests that different pharmacotherapeutic approaches might be more effective than those that are useful in standard PTSD treatment.

5. Ethnopharmacological concerns have rarely been addressed. Lin, Poland, Anderson, and Lesser (1996) have shown that Caucasian versus Asian patients exhibit different pharmacokinetic responses to the same dose of the same drug. Furthermore, dietary habits, beliefs about drug efficacy, and social/familial factors affecting compliance all suggest that ethnocultural concerns must be considered when prescribing a drug for PTSD.

6. We continue to search for a "magic bullet" for PTSD—a single drug that will alleviate all symptom clusters with equal efficacy. Although that is a reasonable goal, it may not turn out to be a practical one. Much published literature suggests that certain drugs may be more effective against some PTSD clusters than others. For example, it has been suggested (Friedman & Southwick, 1995) that MAOIs/TCAs are best for reexperiencing symptoms, SSRIs for avoidant/numbing symptoms, and clonidine/propranolol for hyperarousal symptoms. Should this turn out to be the case, the best approach might consist of individualized selection from an array of drugs with complementary actions rather than a single "magic bullet." There is plenty of precedent for such an approach in standard medical treatment. For example, some patients with arteriosclerotic cardiovascular disease may require a diuretic, a calcium channel blocker, and digoxin. As we learn more about the complex pathophysiology of PTSD, we may also conclude that such an approach may provide the most cost-effective treatment for some of our patients.

SUMMARY

Currently, we know four things with certainty about pharmacotherapy for PTSD:

1. Many people are receiving medication.
2. Clinical trials usually show that some patients benefit greatly from pharmacotherapy.
3. SSRIs are currently the best established drug treatment for PTSD and can be recommended as a first-line treatment.
4. Much more research is needed.

At a more speculative level, drugs seem to have at least three potential benefits for PTSD patients: amelioration of PTSD symptoms; treatment of comorbid disorders; and reduction of associated symptoms that interfere with psychotherapy and/or daily function.

Treatment of PTSD

Table 5.4 summarizes our recommended use of drugs for PTSD treatment. It shows the strength of evidence (AHCPR Level A–F) to support these recommendations as well as specific indications, contraindications, and other pertinent information about each drug. A brief summary of Table 5.4 can be found in "Practice Guidelines for Pharmacotherapy" (Part II of this volume). The most substantial available evidence supports the use of the broad category of antidepressant medications, especially SSRIs, that appear to promote global improvement in most, but not all, randomized clinical trials. It is not as clear whether antidepressants are effective treatment for specific (intrusive, avoidant/numbing, or arousal) PTSD symptom clusters or whether they have a broad spectrum of action against all PTSD symptoms and associated symptoms of depression and anxiety disorders.

SSRIs clearly appear most promising for benefiting all three symptom clusters in civilian PTSD populations. Results with chronic veteran populations are much more difficult to interpret because of the severity and chronicity of their PTSD. TCAs and MAOIs have produced modest, substantial, therapeutic benefits, respectively, in drug trials with veterans, although relatively few patients have participated in such trials. These studies have not been replicated because there has been little active research interest in TCAs or MAOIs in recent years, since SSRIs appear to have advantages with respect to efficacy and tolerability.

Antiadrenergic agents such as clonidine, guanfacine, and propranolol may prove to ameliorate arousal and reexperiencing symptoms by reducing the excessive adrenergic activity associated with PTSD. Unfortunately, at present very little clinical data substantiate this speculation. Anticonvulsants

TABLE 5.4. Evidence for Efficacy of Drugs in the Treatment of PTSD Based on the Published Literature

Drug class	Specific drugs	Strength of evidence[a]	Indications	Contraindications	Remarks
SSRIs	Sertraline[b]	A	• Reduce B, C, and D symptoms. • Produce clinical global improvement. • Effective treatment for depression, panic disorder, and obsessive–compulsive disorder. • Reduce associated symptoms.	• May exacerbate insomnia and agitation. • May produce sexual dysfunction	• Current evidence is stronger for SSRI efficacy among civilian rather than Vietnam veteran cohorts.
	Fluoxetine	A/B			
	Paroxetine	B			
	Fluvoxamine	B			
Other serotonergic	Trazodone	C	• Trazodone/nefazodone may reduce B, C, and D symptoms. • Trazodone is synergistic with SSRIs and reverses SSRI-induced insomnia. • Effective antidepressants, few side effects.	• May be too sedating.	• Very few published reports on either of these agents.
	Nefazodone	B			
	Cyproheptadine	F	• Reduces flashbacks and nightmares.	• Sedation	• Supporting data are anecdotal.
	Buspirone	F	• Reduces B and D symptoms.		• Supporting data are anecdotal.

(continued)

TABLE 5.4. *(continued)*

Drug class	Specific drugs	Strength of evidence[a]	Indications	Contraindications	Remarks
Antiadrenergic	Clonidine	C	• Reduces B and D symptoms.	• May lower blood pressure or slow pulse rate too much.	• Few studies. • Tolerance may develop to clonidine.
	Guanfacine	C	• Reduces B and D symptoms.	• Must use cautiously with patients on hypotensive medications.	• Anecdotal evidence.
	Propranolol	C	• Reduces B and D symptoms.	• May produce depressive symptoms or psychomotor slowing.	• Few studies. • Some negative results.
MAOIs	Phenelzine	A/B	• Reduces B symptoms. • Produces global improvement. • Effective antidepressant and antipanic agent.	• Patients must follow a strict dietary regimen. • Contraindicated in patients with alcohol/substance abuse/dependency. • May produce insomnia, hypotension, and anticholinergic and hepatotoxic side effects.	
	Moclobemide	B	• Reduces B and C symptoms.	• May produce insomnia, headache, dizziness, fatigue, nausea, and diarrhea.	• Only one open trial to date. • Not available in United States. • No dietary restrictions.

TCAs	Imipramine	A	• Reduce B symptoms. • Produce global improvement. • Effective antidepressant and antipanic agents.	• Anticholinergic side effects. • May produce EKG abnormality. • May produce hypotension, arousal, or sedation.	• Not as effective as SSRIs or MAOIs with civilian cohorts. • May be more effective with Vietnam veteran cohorts. • Desipramine was ineffective in a randomized clinical trial.
	Amitriptyline	A			
	Desipramine	A			
Benzodiazepines	Alprazolam	B	• Reduce D symptoms only. • Effective anxiolytics and antipanic agents.	• Should not be prescribed to patients with past or present alcohol/drug abuse/dependency. • May exacerbate depressive symptoms.	• Few studies. • Specific usefulness in PTSD not well established.
	Clonazepam	C			
Anticonvulsants	Carbamazepine	B	• Effective on B and D symptoms. • Effective in bipolar affective disorder.	• May produce neurological symptoms, luekopenia, hyponatremia, and thrombocytopenia.	• Open but no randomized trials for either drug. • May have a unique role in PTSD with comorbid bipolar (and possibly unipolar) affective disorder.
	Valproate	B	• Effective on C and D symptoms. • Effective in bipolar affective disorders.	• May produce gastrointestinal problems and tremor.	
Antipsychotics	Thioridazine	F	• Possible effectiveness on B and D symptoms. • Effective antipsychotic agents.	• Sedation, hypotension, and anticholinergic effects. • Extropyramidal effects (thioridazine primarily).	• Anecdotal reports only. • Not first-line drugs in PTSD but may have unique role for hypervigilant/paranoid, extremely agitated or psychotic patients refractory to other drugs.
	Clozapine	F			
	Risperidone	F			

[a]Level A, randomized clinical trials; Level B, well-designed clinical studies without randomization or placebo comparison; Level C, service and naturalistic clinical studies, combined with clinical observations that are sufficiently compelling to warrant use of this drug; Level F, a few observations that have not been subjected to clinical or empirical tests.
[b]Approved by FDA as an indicated treatment for PTSD (December 1999).

have also shown promise in open clinical trials. Empirical evidence suggests that benzodiazepines are not useful for treating DSM-IV B or C PTSD symptoms. Finally, there is no evidence to recommend antipsychotic agents for monotherapy of PTSD.

Treatment of Comorbid Disorders

A great deal of evidence suggests that pharmacotherapy will successfully reduce most disorders that are comorbid with PTSD. SSRIs, TCAs, and MAOIs have proven efficacy against depression and panic disorder. SSRIs are also effective treatment for obsessive–compulsive disorder and alcohol abuse/dependence. Anticonvulsants are useful in bipolar affective disorder, and propranolol has been shown to be effective in panic disorder.

Treatment of Associated Disruptive Symptoms: Drugs as an Adjunct to Psychotherapy

Since compelling and consistent evidence exists demonstrating the efficacy of cognitive-behavioral treatment for PTSD, medication need not always be considered a first-line intervention. When disruptive symptoms interfere with a patient's ability to participate in psychotherapy, pharmacotherapy has an important potential role as an adjunct to psychotherapy. SSRIs are effective in this regard, since they have been shown to reduce impulsivity, mood lability, irritability, aggressiveness, and suicidal behavior. Antiadrenergic drugs reduce arousal and, possibly, dissociative symptoms. Anticonvulsive mood stabilizers such as carbamazepine or valproate might also be expected to reduce aggressive and impulsive behaviors. And atypical antipsychotics might significantly reduce hypervigilant/paranoid behavior, but there is very little current evidence demonstrating such efficacy with PTSD patients.

The recent development of SSRIs and other novel drugs that might be expected to reduce psychobiological abnormalities associated with PTSD has ushered in a new interest in pharmacotherapy for this disorder. There is good reason to anticipate exciting breakthroughs in the foreseeable future that should equip clinicians with a greater variety of effective drugs that will benefit patients with PTSD.

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